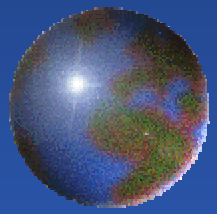
The Risk-Based Outlook for Internationally Harmonized CGMPS



9th Annual GMP By The Sea

August 24, 2004

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Presentation Overview

- CGMPs for pharmaceuticals & biological products
- Driving Forces
- Industry Issues
- FDA Issues
- FDA Approach
- ICH Activities
- Challenges
- An Approach
- Summary

Driving Forces For Harmonization

- Globalization of Pharmaceuticals/ Biologics
- Legal [FDAMA1997 Section 803 (21USC383)]
  - …reduce the burden of regulation and harmonize regulatory requirements …such harmonization continues consumer protections consistent with the purposes of the Act."
  - "…shall support… in efforts to move towards the acceptance of mutual recognition agreements relating to the regulation of drugs, biological products…and the regulation of GMP between the EU and US."
  - "…participate in meetings with representatives of other foreign governments to discuss and reach agreement on other methods and approaches to harmonize regulatory requirements."
  - "… make public a plan for achieving mutual recognition of GMP inspections."
- Trade Facilitation, not Restriction

Driving Forces For Harmonization

- Resource Expenditure/ Limitations
- Ongoing Collaborative Activities
- Ongoing Harmonization Infrastructure

- *Modernization of Pharmaceutical Manufacturing*

Industry CGMP Issues

- Differing regional GMPs and interpretations – lead to inconsistencies
- Difficulty and delay in implementing process improvements - especially global implementation
- More science-based approach in inspections
- Better use of risk assessments in regulatory decision making
- Multiple inspections from regulatory authorities
- **Greater Harmonization, New Paradigms**

FDA CGMP Issues

- Enhancing the public health, maintaining consumer protections
- Accessibility
- GMP Initiative For The 21st Century
  - Quality of Pharmaceutical Products
    - CGMP, Review
  - Analysis – GMP Requirement, Approach to Harmonization
  - Emphasis on Quality Systems
  - Emphasis on Formalized Risk Management
  - Integrative, science-based approach
- Resources
- Variety of established and developing products

FDA Approach to CGMP Harmonization

- "Confidence Building Activities"
- Communication
- Participation/ Harmonization in Quality/ CGMP Activities
  - ICH, PIC/S, WHO
  - Developing harmonized principles and technical requirements
- Informational Exchange
  - Memorandum of Understanding (MOU)
  - Exchange of regulatory and scientific information within legal constraints
    - inspection information, recall information, adverse events
  - Mutual Recognitions Agreement (MRA)

Int.Conference on Harmonization (ICH)

- Members
  - Industry & Regulatory Experts
  - EU, JP, USA, Canada, Observers (e.g., Swiss, WHO)
- Focus - development/ maintenance of guidelines for for marketing authorization
  - Guidance documents
  - Disciplines - Quality, Safety, Efficacy Multidisciplinary
  - Chemical Drugs and Biotechnology Products
    - Can be adopted for other product classes – discretion regional regulatory authorities)
- Adopted outside of ICH regions – sometimes modified

ICH Quality Activities

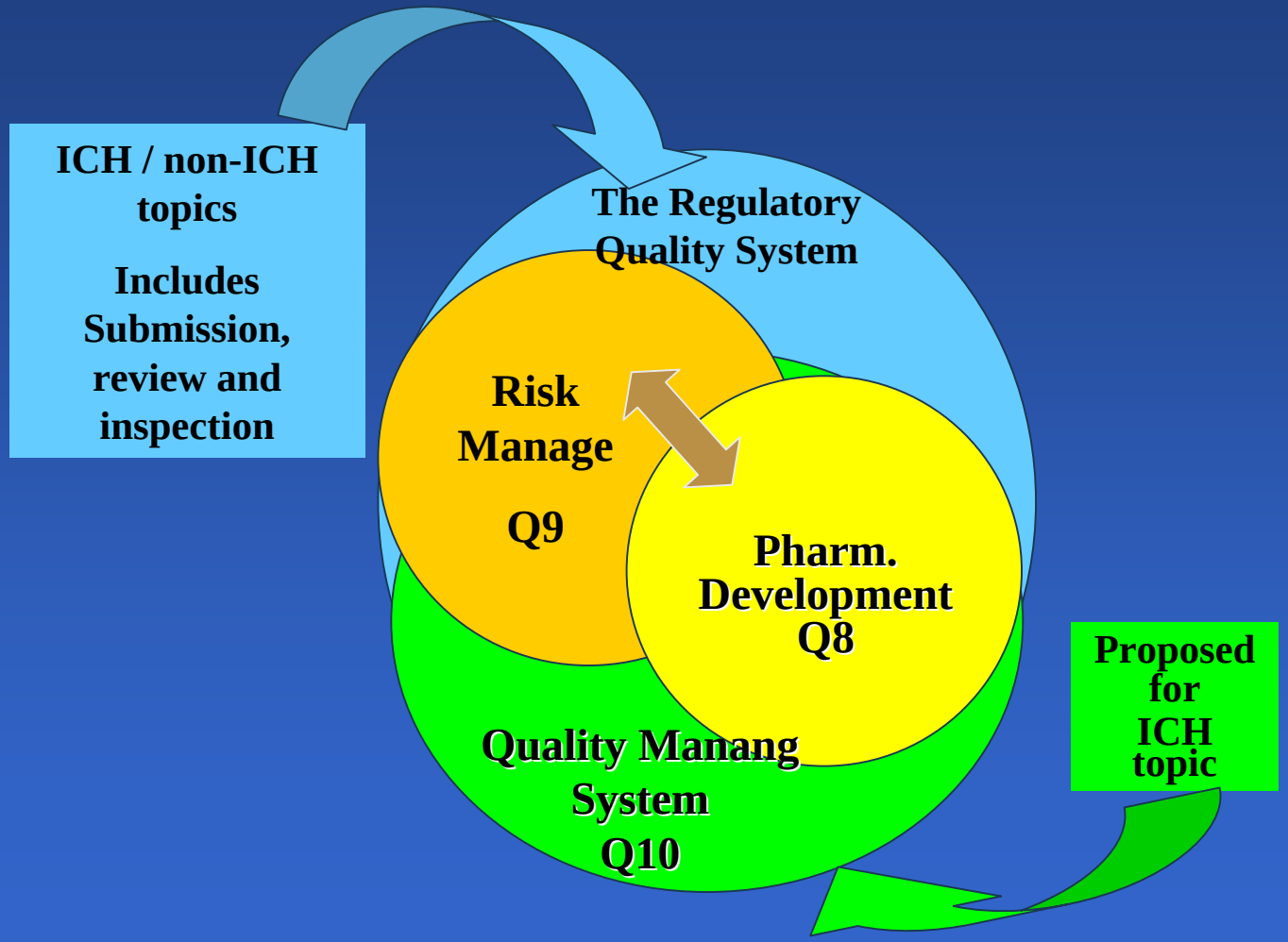
- Q1 Stability
- Q2 Validation
- Q3 Impurities
- Q4 Pharmacopia Harmonization
- Q5 Biotechnology
- Q6 Specifications
- Q7 “CGMP For API” November 2000
- Q8 “Pharmaceutical Development”
- Q9 “Quality Risk Management”
- Q10 Quality Management

Quality Management Q10

- Result of industry scoping exercise
- Proposed ICH Concept Paper
- Integrated Quality Management System
  - Change management
  - Measuring and monitoring change
  - Deviations, investigations, audits, CAPA
- Improved process control and quality management should facilitate continuous improvement

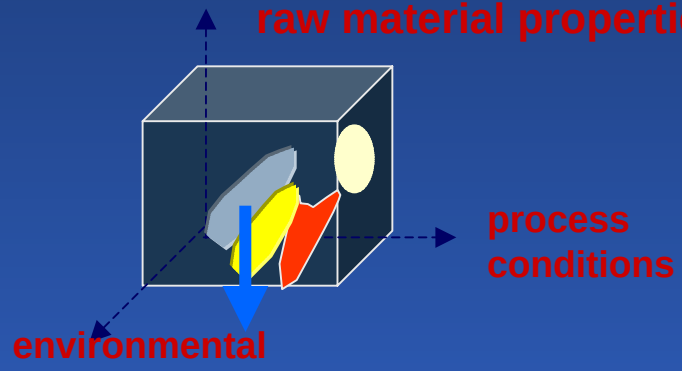
Proposed Pharmaceutical Quality System

Integrated approach



Integration & Consequences

Q8



Q9

Risk Management

Q10

Quality Management

Biotech and Biological Products

- Biotech
  - "Newer and different"
    - Use of technologies and control (manufacturing variability)
    - Need to understand underlying science
- Biologics
  - Other factors – characterization, usage
  - Recent - improvement modern manufacturing
- Science-based, sharing of information
- Within FDA, integrative approach to CMC and CGMP activities
- Should be able to utilize Q9, Q10
- Strong emphasis on global involvement

Challenges to CGMP Harmonization

- Implementation
  - Optional Component of Pharmaceutical Development vs. standard approach (as defined by Q8)
  - Implemented for some products, existing products
  - Will this impact risk and therefore frequency/ extent of inspections - product, site?
  - Reviewer and inspector tool - what is reviewed in submission? on site? updated?
- "Newer" Paradigms - Review and Inspection
  - Product Specialists on Inspections
  - Process Analytical Technologies
  - Team Biologics, Pharmaceutical Inspectorate

Review and Inspection Activities

CMC

Verify CMC

CMC

cGMP

cGMP

Submission

Inspection

Q8 Pharm Development

Challenges to CGMP Harmonization

- Exchange of Information
  - Legal Considerations
    - Protection of Trade Secrets Information
    - Protection of Confidential Commercial Information
- Variety of information exchanged – all can be useful, but to what extent?
- The utility and reliability of information provided depends upon the type and quality of information provided
- Determination of Equivalency - MRA

Challenges to CGMP Harmonization

- Effective & Consistent Inspections
  - Approach (e.g., systems based)
  - Emphasis on:
    - Manufacturer's Quality System
    - Risk Management/ Mitigation
    - Scientific Emphasis
    - Harmonized principles and technical practice, and inspection performance

Challenges to CGMP Harmonization

- Consideration for effective Quality System for CGMP activities
  - Important elements
    - Continual interaction
    - Communication, joint activities, joint training
    - Technical Harmony/ Dispute Resolution

Challenges to CGMP Harmonization

- Principles, Practices, Performance
- Involvement on a Global Basis
  - Countries outside of ICH process
    - Do they follow ICH lead?
    - Do they utilize ICH documents– with modifications?
- Multiple entities involved in some aspect of CGMP
  - National/ regional regulatory authorities
  - Associations (e.g., ICH, WHO, PIC/S, ASEAN, PANDRH)

Challenges to CGMP Harmonization

- More similarities than differences
- Remaining Differences
  - Approaches
  - Technical Considerations
    - Process Validation
    - Aseptic Processing
    - EU Clinical Trials Directorate/ FDA CGMP Approach for Developmental Phase 1-3 IND
- How does FDA determine its involvement?

Pharm. Inspectorate Convention Scheme PIC/S

- GOAL “To lead in the international development, implementation and maintenance of harmonized CGMP standards and Quality Systems of inspectorates in the field of medicinal products”
- Informal co-operative arrangement among regulatory authorities
  - 27 member countries, several applicants
  - Membership requires detailed assessment
  - Annual reassessment of equivalence
- Observers (WHO, Industry)
- FDA is an observer in several areas

Pharm. Inspectorate Convention Scheme PIC/S

- PIC/S functions include
  - Encourage international harmonization of CGMPs
  - Promote uniform interpretation of CGMPs
  - Facilitate exchange of information between members
    - Expert Circles
    - Database of cGMP inspections
  - Develop guidance documents - not binding
  - Forum for training - seminars
  - Develop and promote quality system for inspectors

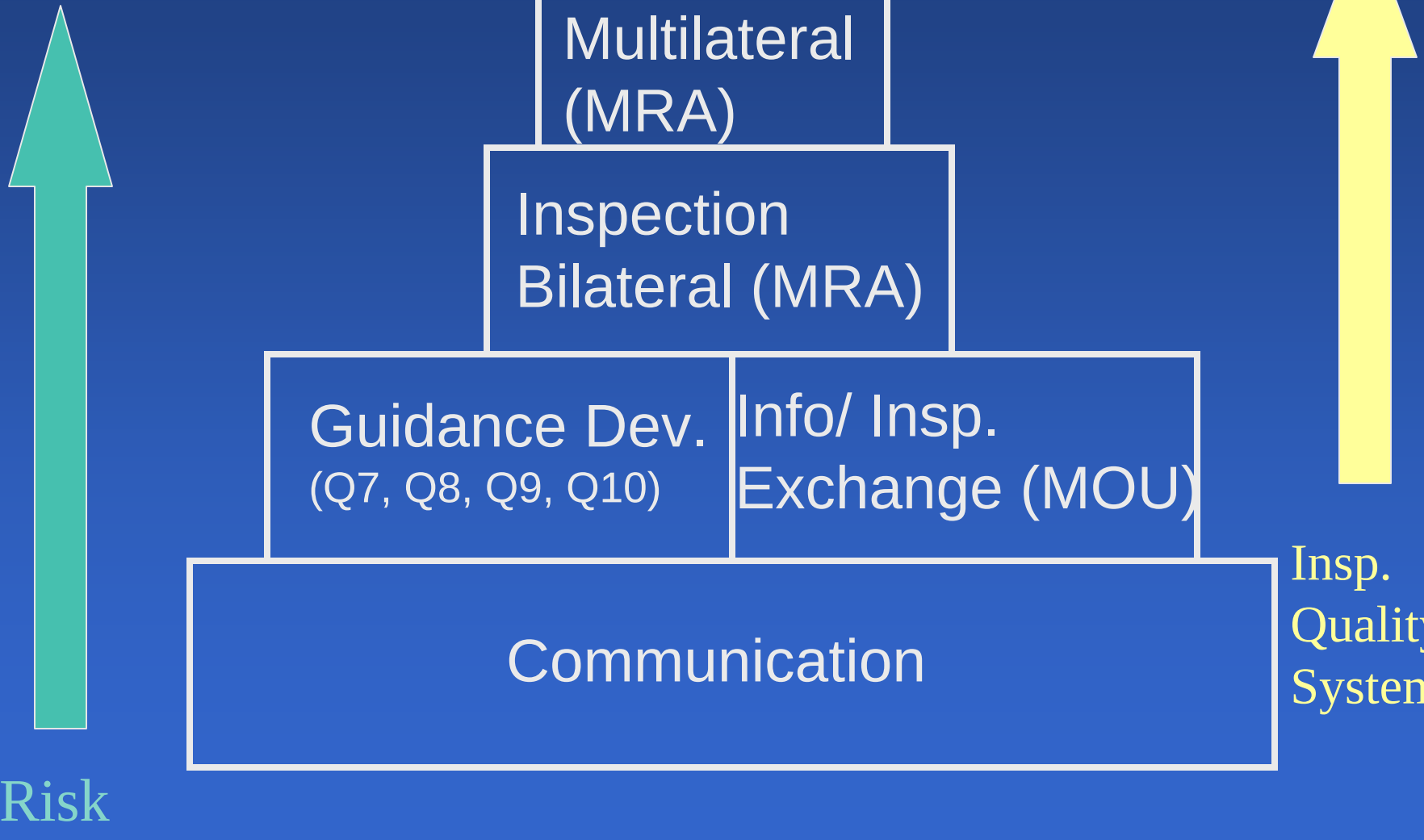
World Health Organization

- Promotes World Health
  - Essential medicines - priority health care needs of the population
- WHO Certification Scheme - Export of essential medicines “competent authority”
- CGMP
  - Develops standards and guidance
  - Facilitate CGMP training
- Strong emphasis on Quality System

An Approach to Harmonization

	Inspection (MRA)	
CGMP Guidance. (Q7,Q8,Q9,Q10)	Communication Info. Exchange (MOU)	Communication Insp. Exchange (MOU)
Communication	Communication	Communication
Organizations	Bi/ Multilateral Countries Organizations	Bi/ Multilateral Countries Organizations

An Approach to Harmonization



Summary

- Drivers for harmonization of CGMP are strong
- Harmonization efforts will continue and will use multiple approaches and venues appropriate for the activity and product
- Initiatives and emphasis on Risk Management and Quality Management provide important fundamentals in structuring and interpreting CGMP and can facilitate further CGMP harmonization

Summary

- An effective Quality System for manufacturers and regulators is critical for consistent product quality and consistent CGMP activities. It is also essential in moving to higher levels of harmonization.
- The Devil is always in the details, although typically not insurmountable
- Assuring the public health is the primary concern of all involved in the manufacture and regulation of pharmaceutical and biological products.